

## **Amendments to the Claims**

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. (Currently amended) A method for inhibiting immunoglobulin-induced toxicity in a subject, comprising administering an immunoglobulin to a said subject, said immunoglobulin having a variable region and a constant region, said immunoglobulin being modified prior to administration by structurally altering multiple toxicity-associated regions in the CH<sub>2</sub> domain of said constant region so that immunoglobulin-induced toxicity is inhibited in said subject, wherein said multiple toxicity-associated regions ~~consist of~~ are localized to amino acids 231-238 and amino acids 310-331 of said CH<sub>2</sub> domain.
2. (Currently amended) A method for inhibiting immunoglobulin-induced toxicity in a subject, comprising administering a structurally altered antibody to a said subject, said structurally altered antibody comprising a variable region and a constant region, wherein multiple toxicity-associated regions in the CH<sub>2</sub> domain of said constant region are modified so as to render said constant region unable to mediate an antibody dependent cellular cytotoxicity response or activate complement, thereby inhibiting immunoglobulin-induced toxicity, wherein said multiple toxicity-associated regions ~~consist of~~ are localized to amino acids 231-238 and amino acids 310-331 of said CH<sub>2</sub> domain.
3. (Currently amended) A method for inhibiting immunoglobulin-induced toxicity in a subject, comprising administering an Ig fusion protein to a said subject, said Ig fusion protein having multiple structurally altered toxicity-associated regions in the CH<sub>2</sub> domain of the constant region of said Ig fusion protein, wherein said multiple structurally altered toxicity-associated regions ~~consist of~~ are localized to amino acids 231-238 and amino acids 310-331 of said CH<sub>2</sub> domain.
4. (Currently amended) A method for inhibiting immunoglobulin-induced toxicity in a subject, comprising administering an Ig fusion protein to a said subject, said Ig fusion protein comprising a modified constant region, the modification being a structural alteration in

multiple toxicity-associated regions within the CH<sub>2</sub> domain of said constant region, wherein said multiple toxicity-associated regions ~~consist of~~ are localized to amino acids 231-238 and amino acids 310-331 of said CH<sub>2</sub> domain.

5. (Currently amended) A method for inhibiting immunoglobulin-induced toxicity in a subject, comprising:

- (a) selecting an immunoglobulin which recognizes and binds a target, said target being associated with a disease;
- (b) mutating said immunoglobulin so selected by structurally altering multiple toxicity-associated regions in the CH<sub>2</sub> domain of the constant region of said immunoglobulin, thereby creating a structurally altered immunoglobulin;
- (c) administering said structurally altered immunoglobulin of step (b) to a said subject under conditions so that said structurally altered immunoglobulin recognizes and binds said target,  
wherein said multiple toxicity-associated regions ~~consist of~~ are localized to amino acids 231-238 and amino acids 310-331 of said CH<sub>2</sub> domain.

6. (Currently amended) A method for inhibiting immunoglobulin-induced toxicity in a subject, comprising:

- (a) selecting an Ig fusion protein which recognizes and binds a target, said target being associated with a disease;
- (b) structurally altering multiple toxicity-associated regions in the CH<sub>2</sub> domain of the constant region of said Ig fusion protein so selected;
- (c) administering the structurally altered Ig fusion protein of step (b) to a said subject under conditions so that said structurally altered Ig fusion protein recognizes and binds said target,  
wherein said multiple toxicity-associated regions ~~consist of~~ are localized to amino acids 231-238 and amino acids 310-331 of said CH<sub>2</sub> domain.

7. (Cancelled)

8. (Previously presented) The method of claim 1 or 5, wherein said immunoglobulin is IgG.

9. (Previously presented) The method of claim 1 or 5, wherein said immunoglobulin is IgM.

10. (Previously presented) The method of claim 1 or 5, wherein said immunoglobulin is IgA.

11. (Previously presented) The method of claim 2, wherein said antibody recognizes and binds Le<sup>y</sup>.

12. (Previously presented) The method of claim 5, wherein said immunoglobulin recognizes and binds Le<sup>x</sup>.

13. (Previously presented) The method of claim 2, wherein said antibody is monoclonal antibody BR96 produced by the hybridoma HB 10036 as deposited with the ATCC.

14. (Previously presented) The method of claim 2, wherein said antibody is chimeric antibody ChiBR96 produced by the hybridoma HB 10460 as deposited with the ATCC.

15. (Previously presented) The method of claim 1 or 5, wherein said immunoglobulin recognizes and binds Le<sup>y</sup>.

16. (Previously presented) The method of claim 1 or 5, wherein said immunoglobulin recognizes and binds to Le<sup>x</sup>.

17. (Previously presented) The method of claim 1 or 5, wherein said immunoglobulin is monoclonal antibody BR96 produced by the hybridoma HB 10036 as deposited with the ATCC.

18. (Previously presented) The method of claim 1 or 5, wherein said immunoglobulin is

chimeric antibody ChiBR96 produced by the hybridoma HB 10460 as deposited with the ATCC.

19. (Previously presented) The method of claim 3, 4 or 6, wherein said Ig fusion protein recognizes and binds Le<sup>Y</sup>.

20. (Previously presented) The method of claim 3, 4, or 6, wherein said Ig fusion protein recognizes and binds Le<sup>X</sup>.

21. (Previously presented) The method of claim 3, 4 or 6, wherein said Ig fusion protein comprises the antigen binding site of monoclonal antibody BR96 produced by the hybridoma HB 10036 as deposited with the ATCC.

22. (Previously presented) The method of claim 3, 4 or 6, wherein said Ig fusion protein comprises the antigen binding site of chimeric antibody ChiBR96 produced by HB 10460 as deposited with the ATCC.

23. (Withdrawn) A pharmaceutical composition comprising a pharmaceutically effective amount of a structurally altered immunoglobulin, and an acceptable carrier, the structurally altered immunoglobulin (1) recognizes and binds a target, the target is associated with cancer and (2) has an inactivated CH<sub>2</sub> domain.

24. (Withdrawn) A pharmaceutical composition comprising a pharmaceutically effective amount of structurally altered Ig fusion protein, and an acceptable carrier, the structurally altered Ig fusion protein (1) recognizes and binds a target, the target is associated with cancer and (2) has an inactivated CH<sub>2</sub> domain.

25. (Withdrawn) A method of treating carcinomas in vivo comprising administering to a subject a pharmaceutically effective amount of the composition of claim 23 or 24.

26. (Withdrawn) The method of claim 30, wherein the structurally altered immunoglobulin in the composition is labeled so as to directly or indirectly product a detectable signal

with a compound selected from the group consisting of a radiolabel, an enzyme, a chromophore, a chemiluminescer, and a fluorescer.

27. (Withdrawn) The method of claim 24, wherein the Ig fusion protein in the composition is labeled so as to directly or indirectly product a detectable signal with a compound selected from the group consisting of a radiolabel, an enzyme, a chromophore, a chemiluminescer, and a fluorescer.

28. (Previously presented) The method of claim 2, wherein said antibody is conjugated to a cytotoxic agent.

29. (Previously presented) The method of claim 1 or 5, wherein said immunoglobulin is conjugated to a cytotoxic agent.

30. (Previously presented) The method of claim 3, 4 or 6, wherein said Ig fusion protein is conjugated to a cytotoxic agent.

31. (Previously presented) The method of claim 28, wherein said cytotoxic agent is selected from the group consisting of antimetabolites, alkylating agents, anthracyclines, antibiotics, anti-mitotic agents, and chemotherapeutic agents.

32. (Withdrawn) A method for treating a subject suffering from a cancer, the cancer being characterized as a group of cells having a tumor associated antigen on the cell surface, which method comprises administering to the subject a cancer killing amount of the composition of claim 23 or 24 joined to a cytotoxic agent under conditions which permit the molecule so joined to bind the tumor associated antigen on the cell surface so as to kill the cells so bound thereby curing the subject.

33. (Withdrawn) A pharmaceutical composition comprising a pharmaceutically effective amount of a structurally altered BR96 antibody, the structurally altered antibody having an inactivated  $\text{CH}_2$  domain.

34. (Withdrawn) A method for treating a subject suffering from a proliferative type disease characterized by cells having a BR96 antigen on the cell surface which comprises administering to the subject an effective amount of the composition of claim 33 joined to doxorubicin such that the immunoconjugate binds the BR96 antigen and kills said cells thereby treating the subject.

35. (Withdrawn) A method for inhibiting BR96 (ATCC: HB10036) induced toxicity resulting from immunoglobulin immunotherapy in a subject comprising administering BR96 to the subject, the BR96 molecule being modified prior to administration, the modification comprising the deletion or substitution of at least one amino acid residue in the toxicity associated domain localized to amino acids 310-331 and the deletion or substitution of at least one amino acid residue in the toxicity associated domain localized to amino acids 231-238 so that complement and Fc receptor mediated toxicity is inhibited.

36. (Withdrawn) A method for preventing BR96 (ATCC: HB10036) induced toxicity resulting from immunotherapy for cancer in a subject comprising:

(a) mutating the BR96 polypeptide by the deletion or substitution of at least one amino acid residue in the toxicity associated domain localized to amino acids 310-331 and the deletion or substitution of at least one amino acid residue in the toxicity associated domain localized to amino acids 231-238 so that complement and Fc receptor mediated immunoglobulin-induced toxicity is inhibited in the altered BR96 polypeptide; and

(b) administering the structurally altered BR96 polypeptide of step (a) to the subject under conditions so that the peptide recognizes and binds cancer associated  $Le^y$  antigens, thereby alleviating symptoms associated with the cancer, the structural alterations of the toxicity associated domains thereby preventing BR96 toxicity in the subject.

37. (Withdrawn) A chimeric BR96 antibody having a structurally altered constant region having the CH1 and CH3 domains but not the CH<sub>2</sub> domain, the antibody being designated cBR96- A.

38. (Withdrawn) The chimeric R96 antibody of claim 37 which is expressed by the plasmid having the sequence shown in SEQ ID NO. 10.

39. (Withdrawn) A BR96 antibody having humanized variable and constant regions, wherein the constant region has been structurally altered so that the CH1 and CH3 domains are present but the CH<sub>2</sub> domain is not, the antibody being designated hBR96-2A.

40. (Withdrawn) The BR96 antibody of claim 39 which is expressed by the plasmid having the sequence shown in SEQ ID NO. 12.

41. (Withdrawn) A BR96 antibody designated hBR96-2B having a structurally altered constant region wherein leucine at amino acid position 235 is mutated to alanine and glycine at amino acid 237 is mutated to alanine.

42. (Withdrawn) A BR96 antibody designated hBR96-2C having a structurally altered constant region wherein glutamic acid at amino acid position 318 is mutated to serine; lysine at amino acid position 320 is mutated to serine; and lysine at amino acid position 322 is mutated to serine.

43. (Withdrawn) A BR96 antibody designated hBR96-2D having a structurally altered constant region wherein proline at amino acid position 331 is mutated to alanine.

44. (Withdrawn) A BR96 antibody designated hBR96-2E having a structurally altered constant region wherein leucine at amino acid position 235 is mutated to alanine; glycine at amino acid position 237 is mutated to alanine; glutamic acid at amino acid position 318 is mutated to serine; lysine at amino acid position 320 is mutated to serine; and lysine at amino acid position 322 is mutated to serine.

45. (Withdrawn) A BR96 antibody designated hBR96-2F having a structurally altered constant region wherein leucine at amino acid position 235 is mutated to alanine; glycine at amino acid position 237 is mutated to alanine; and proline at amino acid position 331 is

mutated to alanine.

46. (Withdrawn) A BR96 antibody designated hBR96-2G having a structurally altered constant region wherein glutamic acid at amino acid position 318 is mutated to serine; lysine at amino acid position 320 is mutated to serine; and lysine at amino acid position 322 is mutated to serine; and proline at amino acid position 331 is mutated to alanine.

47. (Withdrawn) A BR96 antibody designated hBR96-2H having a structurally altered constant region wherein leucine at amino acid position 235 is mutated to alanine; glycine at amino acid position 237 is mutated to alanine; glutamic acid at amino acid position 318 is mutated to serine; lysine at amino acid position 320 is mutated to serine; lysine at amino acid position 322 is mutated to serine; and proline at amino acid position 331 is mutated to alanine.

48. (Withdrawn) A nucleic acid molecule which encodes the BR96 antibody of claim 37, 39, and 41-47.

49. (Withdrawn) A cDNA of claim 48.

50. (Withdrawn) A plasmid which comprises the nucleic acid molecule of claim 48.

51. (Withdrawn) A host vector system comprising a plasmid of claim 50 in a suitable host cell.

52. (Withdrawn) A method for producing a protein comprising growing the host vector system of claim 51 so as to produce the protein in the host and recovering the protein so produced.

53. (New) A method for inhibiting immunoglobulin-induced gastrointestinal toxicity in a mammalian subject comprising administering to said mammalian subject a IgG1 immunoglobulin having a variable region and a constant region, said IgG1 immunoglobulin being modified prior to administration by structurally altering multiple toxicity-associated

regions in the CH<sub>2</sub> domain of said constant region so that immunoglobulin-induced gastrointestinal toxicity is inhibited in said mammalian subject, wherein said multiple toxicity-associated regions are structurally altered by mutating amino acids 235 and 237 in said CH<sub>2</sub> domain.

54. (New) The method of claim 53, wherein the IgG1 immunoglobulin is hBR96-2B.

55. (New) A method for inhibiting immunoglobulin-induced gastrointestinal toxicity in a mammalian subject comprising administering to said mammalian subject a structurally altered antibody comprising a variable region and a constant region, wherein multiple toxicity-associated regions in the CH<sub>2</sub> domain of said constant region are modified so as to render said constant region unable to mediate an antibody dependent cellular cytotoxicity response or activate complement, thereby inhibiting immunoglobulin-induced toxicity, wherein said antibody is monoclonal antibody BR96 produced by the hybridoma HB 10036 as deposited with the ATCC.

56. (New) A method for inhibiting immunoglobulin-induced gastrointestinal toxicity in a mammalian subject comprising administering to said mammalian subject a structurally altered antibody comprising a variable region and a constant region, wherein multiple toxicity-associated regions in the CH<sub>2</sub> domain of said constant region are modified so as to render said constant region unable to mediate an antibody dependent cellular cytotoxicity response or activate complement, thereby inhibiting immunoglobulin-induced toxicity, wherein said antibody is chimeric antibody ChiBR96 produced by the hybridoma HB 10460 as deposited with the ATCC.

57. (New) A method for inhibiting immunoglobulin-induced gastrointestinal toxicity in a mammalian subject, comprising administering to said mammalian subject an Ig fusion protein having multiple structurally altered toxicity-associated regions in the CH<sub>2</sub> domain of the constant region of said Ig fusion protein, wherein said Ig fusion protein comprises the antigen binding site of monoclonal antibody BR96 produced by the hybridoma HB 10036 as deposited with the ATCC.

58. (New) A method for inhibiting immunoglobulin-induced gastrointestinal toxicity in a mammalian subject, comprising administering to said mammalian subject an Ig fusion protein having multiple structurally altered toxicity-associated regions in the CH<sub>2</sub> domain of the constant region of said Ig fusion protein, wherein said Ig fusion protein comprises the antigen binding site of chimeric antibody ChiBR96 produced by HB 10460 as deposited with the ATCC.

59. (New) A method for inhibiting immunoglobulin-induced gastrointestinal toxicity in a mammalian subject, comprising:

- (a) selecting an IgG1 immunoglobulin which recognizes and binds a target, said target being associated with a disease;
- (b) mutating said IgG1 immunoglobulin so selected by structurally altering multiple toxicity-associated regions in the CH<sub>2</sub> domain of the constant region of said immunoglobulin, thereby creating a structurally altered immunoglobulin;
- (c) administering said structurally altered immunoglobulin of step (b) to said mammalian subject under conditions so that said structurally altered immunoglobulin recognizes and binds said target,  
wherein said multiple toxicity-associated regions are structurally altered by mutating amino acids 235 and 237 in said CH<sub>2</sub> domain.

60. (New) The method of claim 59, wherein the IgG1 immunoglobulin is hBR96-2B.

61. (New) A method for inhibiting immunoglobulin-induced gastrointestinal toxicity in a mammalian subject, comprising:

- (a) selecting an Ig fusion protein which recognizes and binds a target, said target being associated with a disease;
- (b) structurally altering multiple toxicity-associated regions in the CH<sub>2</sub> domain of the constant region of said Ig fusion protein so selected;
- (c) administering the structurally altered Ig fusion protein of step (b) to said mammalian subject under conditions so that said structurally altered Ig fusion protein recognizes and binds said target,

wherein said Ig fusion protein comprises the antigen binding site of monoclonal antibody BR96 produced by the hybridoma HB 10036 as deposited with the ATCC.

62. (New) A method for inhibiting immunoglobulin-induced gastrointestinal toxicity in a mammalian subject, comprising:

- (a) selecting an Ig fusion protein which recognizes and binds a target, said target being associated with a disease;
- (b) structurally altering multiple toxicity-associated regions in the CH<sub>2</sub> domain of the constant region of said Ig fusion protein so selected;
- (c) administering the structurally altered Ig fusion protein of step (b) to said mammalian subject under conditions so that said structurally altered Ig fusion protein recognizes and binds said target,

wherein said Ig fusion protein comprises the antigen binding site of chimeric antibody ChiBR96 produced by HB 10460 as deposited with the ATCC.

63. (New) A method for inhibiting immunoglobulin-induced gastrointestinal toxicity in a mammalian subject comprising administering to said mammalian subject an IgG1 immunoglobulin having a variable region and a constant region, said IgG1 immunoglobulin being modified prior to administration by structurally altering multiple toxicity-associated regions in the CH<sub>2</sub> domain of said constant region so that immunoglobulin-induced toxicity is inhibited in said mammalian subject, wherein said multiple toxicity-associated regions are localized to amino acids 231-238 and amino acids 310-331 of said CH<sub>2</sub> domain.

64. (New) The method of claim 63, wherein the IgG1 immunoglobulin is selected from hBR96-2B, hBR96-2C, hBR96-2D, hBR96-2E, hBR96-2F, hBR96-2G, and hBR96-2H.